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Roberts, Graham ; Allen, Katie ; Ballmer-Weber, Barbara ; et al

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DOI: https://doi.org/10.1111/cea.13516

PROFESSOR GRAHAM ROBERTS (Orcid ID : 0000-0003-2252-1248)

PROFESSOR KATRINA J ALLEN (Orcid ID : 0000-0002-1921-4493)

DR AUDREY DUNNGALVIN (Orcid ID : 0000-0002-1540-3959)

DR RONALD VAN REE (Orcid ID : 0000-0003-0767-0894)

PROFESSOR PAUL J. TURNER (Orcid ID : 0000-0001-9862-5161)

Article type : Opinion or Debate

Identifying and managing patients at risk of severe allergic reactions to food: report from two iFAAM workshops

Graham Roberts[1,2,3], Katie Allen[4,5,6], Barbara Ballmer-Weber[7,8,9], Andrew Clark[10], Rene Crevel[11], Audrey Dunn Galvin[12], Montserrat Fernandez-Rivas[13], Kate E. C. Grimshaw[1], Jonathan O'B Hourihane[14], Lars K. Poulsen[15], Ronald van Ree[16] Lynn Regent[17] Ben Remington[18], Sabine Schnadt[19], Paul J. Turner[20], E. N. Clare Mills[6]

Affiliations

1. University of Southampton Faculty of Medicine, Southampton, UK

2. NIHR Southampton Biomedical Research Centre, University Hospital Southampton NHS Foundation Trust, Southampton, UK

3. The David Hide Asthma and Allergy Research Centre, St Mary's Hospital, Isle of Wight, UK

4. Murdoch Children's Research Institute, Royal Children's Hospital, Australia

5. Department of Paediatrics, University of Melbourne, Parkville, Australia

6. Institute of Inflammation and Repair, University of Manchester, UK

7. Allergy Unit, Department of Dermatology, University Hospital, University of Zurich, Zurich, Switzerland

8 Faculty of Medicine, University of Zürich, Zürich, Switzerland

9. Clinic for Dermatology and Allergology, Kantonsspital St. Gallen, St. Gallen, Switzerland

10. Cambridge University Hospitals NHS Foundation Trust, Cambridge, UK

11. René Crevel Consulting Ltd, Bedford, UK; Formerly: Safety and Environmental Assurance Centre, Unilever, Colworth Science Park, Sharnbrook, Bedford, UK

12. Applied Psychology and Paediatrics and Child Health, University College Cork, Cork, Ireland

13. Servicio de Alergia, Hospital Clınico San Carlos, IdISSC, ARADyAL, Universidad Complutense, Madrid, Spain

14. Paediatrics and Child Health, University College Cork, Cork, Ireland

15. Allergy Clinic, Copenhagen University Hospital at Gentofte, Copenhagen, Denmark

16. Departments of Experimental Immunology and of Otorhinolaryngology, Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands

17. The Anaphylaxis Campaign, Farnborough, UK

18. TNO, Zeist, The Netherlands

19. German Allergy and Asthma Association, Mönchengladbach, Germany

20. Section of Paediatrics (Allergy and Infectious Diseases), Imperial College London, London, UK

Address for correspondence

Professor E. N. Clare Mills, PhD, Institute of Inflammation and Repair, Manchester Academic Health Science Centre, Manchester Institute of Biotechnology, University of Manchester, 131, Princess St, Manchester M1 7DN, United Kingdom. E-mail: clare.mills@manchester.ac.uk.

Word count: currently 4500

Key words: allergy, anaphylaxis, co-factors, food, severity

Abstract

Food allergy affects a small but important number of children and adults. Much of the morbidity associated with food allergy is driven by the fear of a severe reaction, and fatalities continue to occur. Foods are the commonest cause of anaphylaxis. One of the aims of the European Union funded Integrated Approaches to Food Allergen and Allergy Risk Management (iFAAM) project was to improve the identification and management of children and adults at risk of experiencing a severe reaction. A number of interconnected studies within the project have focused on quantifying the severity of allergic reactions; the impact of food matrix, immunological factors on severity of reactions; the impact of co-factors such as medications on the severity of reactions; utilising single dose challenges to understand threshold and severity of reactions; and community studies to understand the experience of patients suffering real-life allergic reactions to food. Associated studies have examined population thresholds, and co-factors such as exercise and stress. This paper summarises two workshops focused on the severity of allergic reactions to food. It outlines the related studies being undertaken in the project indicating how they are likely to impact on our ability to identify individuals at risk of severe reactions and improve their management.

Background

Food allergy affects around 5% of preschool children and 2% of school children and adults (1). The prevalence has increased in recent decades with a doubling in peanut allergy (2) and similar increases in hospitalisations due to anaphylaxis in Europe, USA and Australia (3). Food allergy is the commonest cause of anaphylaxis (4), a systemic and potentially life-threatening allergic reaction (5). Anxiety surrounding the fear of a severe allergic reaction has a major impact on food-allergic patients and their families. For example, impaired quality of life is seen with the necessary avoidance strategies, need to carry rescue medication and the associated fear of an allergic reaction (6). Food-induced allergic reactions result in many presentations to hospital each year and there are, often well publicised, cases of fatal anaphylaxis (7). Unfortunately these severe allergic reactions are not predictable (8), and individuals with the same food allergy can have very different reactions following ingestion due to co-factors (3,9). Such co-factors include, among others, exercise, viral infections and several medications, whose presence around the time of reaction may be associated with the development of more severe symptoms. The risks associated with having food allergy are primarily described by the risk of having a severe allergic reaction. The management of patients with food allergy is also driven by risk. With increasing risk, more rigorous avoidance strategies are recommended and adrenaline auto-injectors are prescribed to manage any future severe allergic reactions (5).

Integrated Approaches to Food Allergen and Allergy Risk Management (iFAAM) is a European Union funded FP7 project. iFAAM aims to reduce the burden of food allergy through a number of integrated activities. The project has developed evidence-based approaches and tools to improve both the management of allergens in food as well as the management of food allergy. Many of these activities are focused on the severity of allergic reactions. This paper is a summary from two workshops. Firstly an iFAAM workshop held in Rome, Italy on Saturday 15th October 2016. The aims of the workshop were to consider how best to (i) identify patients at risk of severe reactions and situations that may impact on severity of reaction, and (ii) manage patients at risk of severe reactions, particularly around high risk situations. Secondly a ILSI Europe Food Allergy Symposium held in Madrid, Spain between 18th and 20th April 2018 where the final iFAAM project findings were reviewed and discussed. The paper describes the iFAAM severity activities and how they may lead onto improved allergen and allergy management for consumers with food allergies.

Quantifying the severity of allergic reactions

Allergic reactions to food vary in severity, ranging from isolated oral symptoms, to relatively mild cutaneous and gastrointestinal symptoms and to potentially life-threatening respiratory and cardiovascular features (5). Healthcare professionals use the severity of a reaction to guide treatment for that event and to inform future management of the patients. Being able to accurately assess and describe the symptoms and signs of severe allergic reactions is therefore vital. A number of systems have been developed to quantify the severity of allergic reactions to different agents and in various circumstances, for example: venom (10,11), food (11-18), drugs (19,20) and adverse reactions to allergen immunotherapy (21,22). None are in widespread use, perhaps because none is ideal. They were all developed using expert opinion, and none has been validated. Major limitations of the current schemes include a lack of discrimination between non-anaphylactic reactions of varying severity, lack of applicability to multiple allergen types, and they are not readily translatable into clinical management. For more details, see the recent European Academy of Allergy and Clinical Immunology position paper (23).

To start to address these gaps, iFAAM has developed a Food Allergy Severity Score (FASS) with two linked formats, a numerical nFASS developed with mathematical modelling and an ordinal oFASS developed by experts' consensus with 5 grades that can be reduced to 3 (mild-moderate-severe) to facilitate rapid assessment and ease of communication within most clinical settings. The two scores have undergone internal validation using the EuroPrevall outpatient clinic database (24), and external validation using different data sets that cover different foods, paediatric and adult patients, and the whole spectrum of severity in food allergy. A manuscript covering the development and validation will be submitted for publication in 2019. Further work is planned to validate the system with other allergic triggers.

The availability of an appropriately developed and validated severity scoring tool will have an important impact on patient care. A harmonised approach to defining severity in different populations will allow data from different studies to be directly compared. Given the relationship between past and future severity of reactions, this would allow the development of better prediction models to identify patients at risk of future anaphylaxis. Clinically, the oFASS scale should improve communication of reaction severity between primary care, acute providers and allergy specialists as well as patients. This should enable specialists to better define individuals who may need to take additional precautions. The nFASS is expected to be used as an outcome

measure in research trials; to compare severity between populations and triggers; and to analyse the impact of other factors (as discussed below) and interventions in food allergy severity.

Impact of food matrix on severity (and threshold) of allergic reactions

The food matrix can affect the uptake of nutrients in the same way that the formulation of different drugs may affect their absorption (25,26). This phenomenon results from the physicochemical nature of the food matrix – either the natural structure of plant and animal foods (formed of organelles, cells and tissues), or the fabricated foods (such as gels, dispersions, foams and emulsions). Allergens can also become entrained in the structures formed by these other food components. The food matrix affects the amount of a nutrient in the gut lumen which is available, after digestion, to be absorbed by the body, a property generally known as bio-accessibility (25,26). Coming from the field of molecular nutrition, this concept is relevant to understanding how food allergens are released from food and interact with effector cells in the body to elicit an allergic reaction.

The first description of a matrix effect on clinical reactivity to foods was a repeat food challenge study in four patients where the fat content of a chocolate-based challenge vehicle was increased to 31.5% from 22.9 % (w/w) by the addition of a white, high melting point bakery fat (27). Three patients did not experience the mild oral symptoms that generally precede a reaction and consequently consumed at least a 10-fold higher dose of peanut in the higher fat challenge. These observations led to the hypothesis that the allergen was less bio-accessible in the oral cavity when presented in the higher fat matrix. However, it is likely that the melting point of the chocolate challenge was increased from 29-32°C by the use of a high melting point (47-48°C) fat, as well as altering the fat crystal structure of the chocolate. A comparison of a water continuous chocolate dessert matrix and dark chocolate bars in seven patients with either peanut or hazelnut allergy showed the chocolate bar (35% (w/w) fat) resulted in a higher cumulative threshold dose or reaction than the dessert matrix (8% (w/w) fat) (28). Magnetic resonance imaging (MRI) showed the gastric residence time for the chocolate bar was much longer than the dessert which might explain the delay in development of symptoms during the challenge with the chocolate bar (28). There is also evidence that presentation of allergens in a baked matrix requires a higher dose to be administered to elicit a reaction. For example, cow's milk allergic patients have been found to reacted at lower doses to milk in a screening challenge than they did in the up-dosing for oral immunotherapy with milk in a baked muffin matrix (29). However other studies have failed to

show a similar matrix effect with egg and cow's milk (30,31). An impact on the threshold dose and severity of reactions was also observed in a group of hazelnut allergic patients when capsules were used to deliver challenge doses, rather than a complex pudding matrix (32). In this study the average threshold dose was increased by 3-fold, the lowest observed adverse effect level being increased by 10-fold and eight subjects experiencing no reaction even after consumption of 10g of hazelnut.

Insights are being gained into the mechanisms whereby the food matrix might affect allergen bio-accessibility through *in vitro* digestion studies, using either batch or dynamic models of digestion. An issue remains regarding the validation of such models using human studies, either by analysing the intestinal contents from ileostomy patients or from intubation studies, although the latter are limited to the study of liquid meals because of the constraints of nasogastric sampling. However, studies are lacking directly linking *in vivo* studies on clinical reactivity to foods, and *in vitro* studies investigating bio-accessibility of allergens during mastication and gastro-intestinal digestion, and subsequent uptake into the circulation. It is inevitable that the number of studies where repeat challenges have been undertaken in the same study population are small, and drawing conclusions about matrix effects in populations is difficult and may be misleading, especially if differences in severity of reaction, but not threshold dose are to be defined.

Addressing these gaps is a major objective of the iFAAM project with focus being placed on peanut. The differences between baked matrices (cookies) and a water continuous dessert matrix have been investigated in the iFAAM project. Further studies will be required using the same systematic approach to identify the common rules governing bio-accessibility of food allergens in complex food matrices. Such studies will inform food allergen management plans and support evidence-based risk assessment of novel foods. Such knowledge is crucial to assessing the allergenic risks posed by new technologies, such as 3D printing of foods, and novel functional ingredients being developed to improve nutritional quality of foods and address the grand challenge of food security.

The influence of intrinsic immunological factors on reaction severity

Given the pathophysiology of IgE-mediated reactions, it seems likely that the nature of food allergen-specific IgE plays a role in the severity of a reaction, since IgE is a prerequisite for a

reaction to happen at all. For example, the qualitative nature of the IgE-response determines whether a food allergic person may react to “stable” allergens (i.e. highly abundant digestion- or processing-resistant allergens) such as the storage proteins of peanuts, tree nuts and seeds or to “unstable” allergens such as the PR-10 related allergens cross-reacting with the birch pollen allergen Bet v 1, such as hazelnut Cor a 1.04, apple Mal d 1, or even peanut Ara h 8 (33). The avidity and affinity of the specific IgE-allergen interaction has been associated with the likelihood of an allergic response (34). Together with prior reaction history, this may help to predict the likelihood of a future severe reaction in appropriate individuals. Looking at the specific IgE in a more quantitative manner, such as relating a specific IgE-titre to severity, has generated equivocal results (3).

Immunoglobulins of the IgG-isotype are not considered to play a pathogenic role in food hypersensitivity and their measurement is discouraged as a diagnostic marker for food allergy (5,35). It has however been speculated that non-IgE isotypes - also including IgA - may offer protection from food-induced IgE-mediated reactions, in a manner similar to that believed to occur during allergen-specific immunotherapy. For example, food-specific IgG4 was reported to block *in vitro* reactions in basophils and mast cells to peanut (36). Little is known though as to whether such antibodies provide real-life protection and can reduce severity of food-induced allergic reactions. While this has been observed in studies of tolerance induction, there are few data to indicate whether IgG isotypes are useful either for predicting outcome or severity of allergic reactions at oral food challenge under medical supervision. In the iFAAM project, the prognostic value of specific IgG_4 was studied in a cohort of 137 patients with challenge proven peanut allergy and 25 sensitized tolerant subjects. Although IgG and IgG_4 over IgE ratios were indeed found to be inversely associated with severity of reactions during challenge, they did not predict challenge outcomes better than IgE alone (37).

Following the cross-linking of two or more receptor-bound IgE-molecules by allergens, effector cells - primarily believed to be mast cells - become activated. Basophils may also contribute to reaction severity, with evidence of both basophil activation and basophil trafficking in allergic reactions due venom and food (38). The relationship between basophil activation/trafficking and reaction severity needs to be further explored. Studies of the cellular compartment of IgE-induced reactions, in particular mast cells, have been hampered by the question as to which anatomical site actually constitutes the target organ in food allergy: when a food allergen enters the digestive

tract, is it absorbed systemically and distributed to target organs such as the vascular system, the lungs and the upper airways to induce local mast cell activation? Or does it activate mast cells lining the digestive tract, resulting in the release of inflammatory mediators from the gut which are then distributed systemically? Alternatively, allergen absorption may occur across the buccal mucosa (39), resulting in rapid systemic allergen distribution independent of absorption distal to the mouth: such rapid absorption may explain the observation that anaphylaxis can occur within minutes of ingestion.

Human mast cells originate from hematopoietic stem cells residing in the bone marrow and bear the surface markers CD34, CD117 and CD13. Mast cell progenitors leave the bone marrow and travel by the circulation to the peripheral sites where they home to vascular endothelium and enter peripheral tissues upon recruitment. In the tissue immature lineage mast cells fully develop into mature granule-containing mast cells. The differentiation and maturation of mast cells is directed by cytokines in the local microenvironment. Stem cell factor (SCF) is essential for mast cell differentiation. SCF binds to CD117 (c-kit) and control development and survival of mast cells. Recently published studies have used *in vitro* derived mast cells to delineate a possible correlation between mast cells response to allergen and asthma or atopic status, (40,41). Similar studies would be needed to elucidate whether mast cells from food allergic patients are predisposed to a higher activation level thus determining the severity of reactions in food allergy.

The impact of medications as co-factors in allergic reactions

The severity of allergic reactions to foods varies significantly – even within the same individual – and while differences in the exposure dose may contribute to this observation, severity is clearly impacted upon by a range of other influences (“co-factors”), independent of dose. One co-factor thought to be responsible for increasing the severity of reactions is medications. A knowledge of the impact of specific medications on the severity of allergic reactions may allow us to provide information to affected individuals to help them avoid risky situations.

Proton-pump inhibitors

Gastric enzymes, such as pepsins, require an acidic environment to function. Following treatment with proton-pump inhibitors (PPI), which reduces gastric acidity to pH 4.0 or higher, pepsin becomes less active (42). Theoretically, this may prevent digestion-labile proteins with an

allergenic potential from being fully degraded (43), resulting in sensitisation and the development of clinical allergy. In one study, 5 of 153 patients treated with anti-ulcer medication for three months developed specific IgE to hazelnut and clinical symptoms; three of them developed symptoms under single-blind, placebo-controlled food challenges, with either pruritus or urticaria, and the remaining two upon accidental ingestion, with OAS or urticaria (44). In another report, patients with fish allergy underwent blinded food challenges with fish extract digested with gastric enzymes at pH 2.0 and 3.0. Fish extract digested at pH 3.0 triggered reactions at 10- to 30-fold lower cumulative challenge doses than extract treated at pH 2.0, and two of four patients reacted only to the latter. These data suggest that impaired digestion might put the patients with food allergy at a higher risk of developing symptoms at lower doses and at potential risk of more severe allergic reactions (45). This effect, however, has not yet been demonstrated in a well-controlled, double-blind, placebo-controlled food challenge (DBPCFC) setting, or in a larger study cohort.

Given this, within the iFAAM project the impact of PPI on severity of food-induced allergy symptoms and minimum eliciting dose has been studied at two geographically different centres, Zurich and Madrid in a randomised double-blind placebo-controlled clinical trial (EUDRA CT nr 2015-001863-38), analysing food reactivity by DBPCFC. Patients with walnut allergy have undergone three food challenges (two active, one placebo session) with a pre-treatment with either PPI or placebo. Publication of results is expected in 2019.

Non-steroidal, anti-inflammatory drugs (NSAIDs)

NSAID-enhanced, food-induced, allergic reactions are mainly reported in patients with food-dependent, exercise-induced anaphylaxis (FDEIA) (46) or in Lipid Transfer Protein (LTP)-sensitized individuals from Mediterranean countries. A number of case reports or series have been published (9,47). In a French case-control study, the odds ratios for severe food-induced anaphylaxis associated with aspirin and other NSAIDs were 10.8 and 8.2 respectively (48). A third (11/34) of food-induced anaphylaxis in LTP syndrome patients were cofactor-dependent (mainly NSAID) by history in one recent study (aspirin, ibuprofen, diclofenac, metamizol) (49). In another retrospective study, 58% (43/74) of patients with co-factor-induced mainly LTP-mediated food allergy, NSAID was identified as a major co-factor (50).

In just a few cases, the effect of NSAIDs on the manifestation of food allergy has been assessed *in vivo*. Matsukura (46) observed an anaphylactic reaction in two patients under combined aspirin and wheat challenge and Matsuo (51) observed allergic reactions in three other patients in a similar setting. Brockow *et al.* has investigated aspirin as a cofactor for WDEIA, performing gluten challenges under exercise with aspirin intake but unfortunately aspirin was combined with alcohol as a second and therefore confounding cofactor (52). One hypothesis for the NSAID-related enhancement of food allergy is the induction of increased gastrointestinal barrier permeability by affecting the function of gastric epithelial tight junctions, which may increase the absorption of allergens (53). Elevated gliadin concentration in serum has been observed with NSAID intake in a dose-dependent manner, even in low-dose-aspirin treatment (46,51,52,55). Another hypothesis postulated is a direct NSAID effect on mast cell function (9,56) and basophils (57).

Angiotensin-converting enzyme (ACE) inhibitors and beta-blocking agents

Both drugs have been reported to aggravate allergic reactions (refs) although other studies would disagree (58-62). In a French case-control study, the odds ratios for severe anaphylaxis with co-existing beta-blocker and ACE inhibitors treatment were 6.8 and 13.0 respectively (48). Risk factor analysis in 4783 patients from the anaphylaxis registry of the German-speaking countries calculated a modest but significant increase of odds ratio (OR increase) for the combined use of these drugs (63,64). Comparing patients (adjusted for age and sex) with severity grade I/II versus grade III/IV, there was no significant effect for isolated ACE inhibitor or beta-blocker intake. There was only a significant effect observed for the isolated beta-blocker intake if grades I to III versus grade IV were analysed (64). These data were supported by a mouse model (63). Nevertheless, more studies are needed to assess the impact of ACE inhibitors and beta-blockers on the severity of allergic reactions.

The impact of exercise and physiological stress on severity of allergic reactions

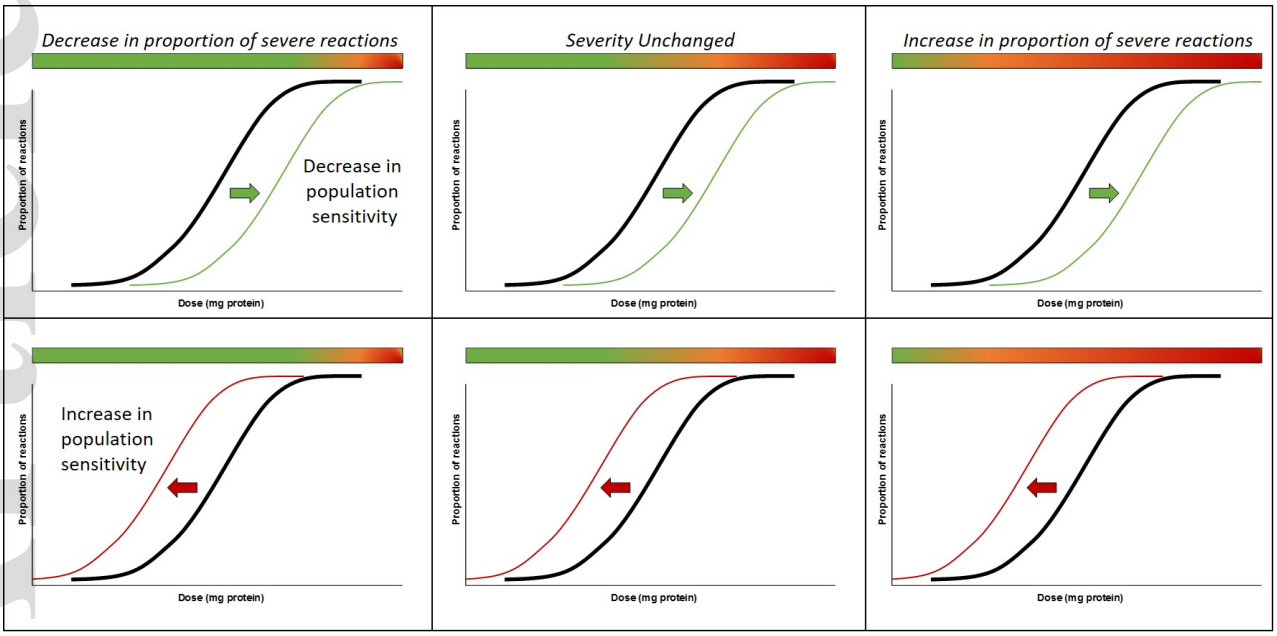
Other potential co-factors are exercise and physiological stress (eg sleep deprivation). They may also be responsible for some of the large variation in severity of allergic reactions in individual patients. One approach to look at this is to focus on threshold doses, the smallest amount of allergen required to induce an allergic reaction in individuals. Population dose-distribution curves describe the proportion of a population with a specific food allergy who will react to increasing doses of the allergen (Figure 1). Co-factors may be able to shift population dose-distribution curves to the left, resulting in a higher proportion of reactions at a lower dose and potentially

increasing the severity of the reaction. Conversely, as described previously, other co-factors may have the opposite effect (e.g. remind readers of one) and shift the dose-distribution curves towards a less sensitive population (Figure 1). Understanding these population-based dose-distribution curves, the factors which might impact upon them, and the magnitude of this effect is crucial to guide the advice about when precautionary allergen labelling (PAL) should be applied to food products. With better informed models, higher reference doses for governmental and industry-based food allergen management programs may be acceptably safe (65).

These questions have led to the development of the Threshold Reactivity Clinical Evaluation (TRACE) Study, associated with the iFAAM consortium and funded by the United Kingdom Food Standards Agency. One hundred peanut-allergic adults are being challenged with peanut: an initial baseline peanut challenge to establish their threshold, and then three further challenges in a random order, including one after sleep deprivation, another with concurrent exercise and a repeat baseline challenge. A comparison of challenges with and without sleep deprivation and exercise will allow within-patient variability on threshold to be determined, as well as any additional impact of sleep deprivation and exercise on the threshold for reactivity. Additionally, the study offers the opportunity to also look at the impact of these co-factors on reaction severity and will provide dose-distribution modelling for a UK adult population.

These data will be important in informing better allergen management in the food industry as they should provide a more robust evidence base for harmonised reference doses and therefore action levels (65). TRACE will report in 2019.

Figure 1. How do extrinsic factors affect threshold and severity of allergic reactions?



Extrinsic factors may influence both the threshold and severity of allergic reactions. They may reduce the threshold dose that induces an allergic reaction in a percentage of the allergic population (bottom line) while reducing (left) or increasing (right) the severity of reactions. Other extrinsic factors may have the opposite effect increasing the threshold dose that induces an allergic reaction in a percentage of the allergic population (top line) and either reducing (left) or increasing (right) the severity of reactions. See also Hourihane and Knulst (66).

What can we learn from single dose challenges?

Population dose-distribution modelling of individual threshold doses can be used to establish public health measures such as the control of PAL. These dose-distribution curves can be used to define reference doses. For example, the dose eliciting a reaction in 1% of individuals with peanut allergy (eliciting dose, ED_{01}) has been estimated to be 0.2 mg peanut protein, using log-normal and log-logistic models (67,68). The ED_{01} was selected by the VITAL Scientific Expert Panel (VSEP) because it is predicted to protect 99% of the peanut-allergic population against any reaction. This dose can be used to inform allergen action levels as decision points to apply PAL. Alternatively a different protection goal could be chosen by using the ED_{05}, the dose at which 95% of the population are protected (69); this has the advantage of giving higher action levels involving potentially fewer products bearing PAL, albeit with more individuals remaining at risk of

allergic reactions to unintentionally present allergen(s). Whatever the reference dose used, it is clearly critical to confirm the benign nature of reactions at that dose, and particularly to ensure that their nature and frequency remain tolerable in public health terms.

It is important that eliciting doses derived from dose-distribution models are validated. The recently completed Peanut Allergen Threshold Study (PATS) has focused on the ED_{05} for peanut in a single dose (66,69). Only 8/375 (2.1%) subjects had convincing objective reactions according to pre-defined criteria, all mild. In iFAAM, the same protocol has been applied to milk, egg and hazelnut to validate the ED_{05} for each of these important allergens, albeit across much wider confidence intervals, owing to smaller numbers of participants.

The single dose challenge protocol has important potential clinical application. It is very easy to use and has been positively received by families, as it is much less time consuming than existing cumulative dose food challenge protocols. Food allergy-related quality of life improved in both non-reactors and reactors (66). ED_{05} reactors could potentially be followed up by another single dose protocol using the ED_{01} to better delineate their personal thresholds. Clinical services without the resources for full cumulative dosing food challenges could use this single dose approach safely, to identify the most dose-sensitive subjects. This could allow advice with regards to PAL to be personalised.

Validation of the log-normal ED_{05} by these single dose studies, will hopefully motivate the scientific, food industry and public health communities to adopt this quantitative approach to decisions to use PAL, starting with the establishment of a defined and widely-accepted reference dose for peanut in quantitative risk assessment. This would underpin a more evidence-based use of PAL, by providing sound scientific evidence to protect the vast majority of the peanut allergic community.

How can community reactions help us to understand severity of allergic reactions?

Clinical reactions to food mostly occur outside the hospital or clinic setting. It is therefore important to explore severity in the community to ensure that similar patterns are seen to those observed in hospital-based studies. Such community studies are challenging, as they are inevitably observational and often retrospective, and reported severity may be prone to bias by

patients' personal perception and experience. The "Allergic Reactions in the Community" (AllerRIC/AlleRiSC: UK, Ireland) and "Allergic Reactions" (AlleREACT: UK, Ireland, Spain, Germany, Poland) studies have attempted to address some of these problems by developing and validating two online reporting tools for food allergic reactions in the community, allowing for reporting of incidents in near real-time (70,71). The AllerRIC/AlleRiSC study uses a multi-method, longitudinal design which allows tracking of the same cohort of adult patients over a two-year period (2014-2016). Adult patients with confirmed food allergies were asked to report their reactions to food regardless of perceived severity, from mild incidents to anaphylaxis. Participants' previous reactions and medical history were recorded in Clinical Record Forms in order to compare the prospective incidence with the retrospective records. Additionally, a measure of perceived severity was included in the reporting tool to explore relationships between perception of severity (from 0 "extremely mild" to 9 "extremely severe) and reported symptoms (70,71). Forty food-allergic incidents were reported in Ireland and the UK between October 2014 and December 2016. Analyses showed a significant relationship between perceived severity, reported symptoms, risk perception, and psychological impact (as measured on 5-item scale adapted from Positive and Negative Affect Scale, PANAS). The related AlleREACT study has gathered real time data via the internet on reactions in adults with food allergy and parents of affected children from the UK, Ireland, Spain, Germany, France, and Poland. To date, over 400 reactions have been reported with a wide variety of severities. Results from these studies will be available in 2019.

Summary and conclusions

Individuals experiencing severe allergic reactions to food make up an important subgroup, they experience considerable morbidity, and while fatal reactions are rare, they are also unpredictable (72,73). Within the iFAAM project, a Food Allergy Severity Score (FASS) has been developed and validated. This has the potential to accurately describe previous allergic reactions at both a simple and more complex level. Several iFAAM studies are examining the impact of the food matrix on reaction severity; this would allow us to highlight which foods are particularly high risk for affected individuals. The presence of co-factors may also impact reaction severity. iFAAM has investigated the effect of proton-pump inhibitors, which are commonly prescribed, on DBPCFC to walnut in a two centre study. The potential impact of exercise and sleep deprivation as co-factors is also being examined in the associated TRACE study. Understanding the magnitude of the impact of these potential co-factors on thresholds and severity will allow us to better advise patients of scenarios which might place them more at risk, and provide guidance to public health

authorities and the food industry on the level of unintended allergen presence in foods that are likely to be safe for most individuals with food allergy. These decisions are being driven by population dose-distribution curves, describing the relationship between dose of allergen and likelihood of reaction; these are being validated by iFAAM using single dose challenges. This approach also has the potential to improve patient experience as it is a relatively simple way of identifying individuals who are likely to react to very small quantities of allergen. Finally iFAAM is also attempting to understand the experience of individuals who have reactions in the community; this will allow us to set the experimental studies in the context of real life and to integrate the impact of biopsychosocial factors, such as physiological and psychological stress, into subsequent multi-system models.

Acknowledgements

We would like to acknowledge the input of many of our iFAAM and other colleagues. For the matrix work: Kirsten Beyer – Berlin; Joan Bartra – Barcelona; Karine Adel-Patient, Herve Bernard – Paris; Harry Wichers – Wageningen; IFR Team: Marianne Defernez, Jack Dainty, Adam Macierzanka, Ana Sancho, Neil Rigby, Alan Mackie; University of Manchester: Ivona Baricevic-Jones, Phil Johnson, Justin Marsh, Rebekah Sayers, Anuradha Balasundaram, Bushra Javed, Charlotte Hands, Carol Ann Costello, Huan Rao, Frances Smith, Phil Padfield; UHSM: Adnan Custovic, Angela Simpson, Aida Semic-Jusufagic, Marina Themis; Allerg-e-lab: Iain Buchan, Phil Couch, Chris Munro, Matt Sperrin. For the severity score: Madrid: Ismael Gómez García, Cristina Fernández Pérez. For the single-dose-challenges: Cork: Yvonne d'Art, June Considine, Gillian Dunngalvin; FARRP: Steve Taylor, Joe Baumert, Julie Nordlee; Madrid: Guadalupe Marco Martín, Ismael Gómez García; Valerie Trendelenburg – Berlin. PATS: Wayne Shreffler. For community studies: Aida Semic-Jusufagic, Christopher Munro, Philip Couch, Marina Themis, Angela Simpson; DAAB, Anaphylaxis Campaign (Moira Austin), AEPNAA (Pilar Hernandez), Yanne Boloh, Anaphylaxis Ireland (Fiona Kenna, Deirdre Galloway). AMC: Mareen Datema, Koos Zwinderman, serge Versteeg, Laurian Jongejan. For the proton pump inhibitor effect: Madrid: Guadalupe Marco Martín, Ismael Gómez García, Isadora Suarez Lorenzo. We would also like to acknowledge the support of ILSI in arranging the second workshop.

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